

REMARKS

This paper is filed in response to the Final Office Action mailed December 9, 2009 (the "Office Action"). The applicants kindly thank the Examiner for the telephone interview on December 4, 2009 and the summary of the interview provided in the Office Action. For the reasons set forth below, applicants submit that each of the pending claims is patentable and in condition for allowance. Therefore, reconsideration of the claims is respectfully requested.

Claim Rejections—35 U.S.C. § 112, First Paragraph

Claims 7-9 and 19-21 are rejected under 35 U.S.C. § 112, First Paragraph. Claims 8, and 19-21 have been cancelled herein thus mooted the rejection thereof. Applicants submit that the as-filed specification of the present application fully enables the current claims. Accordingly, applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, First Paragraph, be withdrawn.

It is asserted in the Office Action that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." (*Office Action*, p.3). However, as is set forth in the Manual of Patent Examining Procedure ("the M.P.E.P."), the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the art without undue experimentation. (*See, M.P.E.P. § 2164.01*, citing *United States v. Telectronics, Inc.*, 857F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). In this case, the teachings and experimental support provided by the specification specifically support the invention as it is recited in the pending claims, allowing one of ordinary skill in the art to not only appreciate the invention, but to make and use the invention as it is claimed.

Applicants submit that at the time of filing one of ordinary skill in the art would have all the information needed to practice the claimed invention without undue experimentation. Independent claim 7 as amended recites a method of inhibiting

migration of human microvascular endothelial cells (HMVECs) expressing a native Robo-4 receptor, the method comprising exposing said HMVECs to a Slit2 ligand or a HMVEC migration inhibiting fragment thereof, wherein exposing said HMVECs to said Slit2 ligand inhibits migration of said HMVECs. Claim 9, depending from claim 7, recites the method of claim 7, wherein exposing said HMVECs to a Slit2 ligand comprises exposing said HMVECs to a human Slit2 ligand or a HMVEC migration inhibiting fragment thereof. The teachings and guidance included in the specification of the present application, including the experimental evidence provided therein, specifically support such methods. In particular, it was stated in previous office actions that the specification is "enabling for a method of inhibiting migration of HMVECs" (*Office Action of February 19, 2009*, page 4), and in the current Office Action, it is acknowledged that the experimental evidence provided in the specification is "enabling for a method of inhibiting the migration of HMVECs in vitro using Slit2 ligand" (*Office Action*, p. 3). When the experimental results detailed in the specification are combined with the specific teachings provided by the specification, such as those found in paragraphs [0042]-[0045] and [0050]-[0052], one of ordinary skill in the art would be equipped with information sufficient to practice the full scope of the methods, including *in vitro* and *in vivo* methods, recited in the pending claims.

It is asserted in the Office Action that, given the unpredictability in the art, the specification would not equip one of ordinary skill with sufficient information to practice the invention in both *in vitro* and *in vivo* contexts. However, applicants reaffirm that the enablement requirement does not dictate that the specification provide working examples describing every embodiment of a claimed invention, only that the specification as a whole allow one of ordinary skill to practice the invention without undue experimentation. (*See, M.P.E.P. § 2164.02*). Again, applicants respectfully submit that the teachings of the specification, particularly in light of the experimental evidence provided therein, specifically enable the subject matter recited in the pending claims. Therefore, applicants kindly request the rejection of claims 7 and 9 under 35 U.S.C. § 112, First Paragraph.

Claim Rejections—35 U.S.C. § 112, Second Paragraph

Claims 19-21 are rejected under 35 U.S.C. § 112, Second Paragraph. Claims 19-21 have been cancelled herein thus mooted the rejection thereof.

Claim Rejections—35 USC § 103

Claims 7-9 and 19-21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Geng (U.S. Pub. No. US 2003/0236210) in view of Goldberg (U.S. Patent No. 5,480,975). Claims 8, and 19-21 have been cancelled herein thus mooted the rejection thereof.

Independent claim 7 as amended recites a method of inhibiting migration of human microvascular endothelial cells (HMVECs) expressing a native Robo-4 receptor, the method comprising exposing said HMVECs to a Slit2 ligand or a HMVEC migration inhibiting fragment thereof, wherein exposing said HMVECs to said Slit2 ligand inhibits migration of said HMVECs. Claim 9, depending from claim 7, recites the method of claim 7, wherein exposing said HMVECs to a Slit2 ligand comprises exposing said HMVECs to a human Slit2 ligand or a HMVEC migration inhibiting fragment thereof. In direct conflict with the current claims, Geng teaches that Slit2 induces the migration of HMVECs. Goldberg is relied upon only as disclosing the stimulation of angiogenesis in hypoxic areas. Applicants submit that Geng teaches directly away from the claimed invention by teaching that Slit2 induces HMVEC migration. Therefore, applicants respectfully submit that claims 9 and 7 are not obvious in view of Geng and Goldberg.

On the bottom of page 10, beginning with line 20, and extending to page 11, line 2, the Examiner alleges that inhibiting the migration of HMVECs expressing native Robo-4 with Slit2 is an inherent function which is obvious from the combination of Geng and Goldberg. However, an unknown inherency cannot be the basis of an obviousness rejection and, at the time of the application, it was not known that Slit2 inhibits HMVEC migration. Again, it must be emphasized that Geng only teaches that Slit2 induces HMVEC migration. As stated in the MPEP § 2141.02(V.), obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established (*In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955).

(Fed. Cir. 1993). Applicants do not acquiesce to the assertion that any portion of the subject matter recited in the pending claims can be inherently found in the teachings of the cited references. Moreover, because the alleged inherency of Slit2 inhibition of HMVECs was not known at the time of the application, and was only established by the current inventors, the current claims could not be found obvious under § 103, and the Examiner's assertions must fail. Therefore, the applicants respectfully request that the rejection of claims 7 and 9 be withdrawn.

Applicants wish to highlight the fact that the concept of inherent anticipation under § 102 simply cannot be applied in the same way to obviousness determinations under § 103. Applicants recognize that the prevailing view of the United States Court of Appeals for the Federal Circuit is that one of ordinary skill in the art is not required to recognize an inherent feature in a prior art disclosure for purposes of anticipation under § 102 (*Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), specifically "reject[ed] the contention that inherent anticipation requires recognition in the prior art"). However, this holding, as well as others addressing inherency under § 102, was discussing inherent anticipation, not obviousness, and, as mentioned above, the analysis for obviousness cannot be based on what is unknown. The suggestion or motivation to combine or modify references required to establish a *prima facie* case of obviousness, **must** occur prior to the application date, and an unknown inherency cannot supply this suggestion or motivation at the required time without resorting to impermissible hindsight. Section 2142 of the MPEP states, that to reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. More specifically, an unknown inherency cannot be a basis for obviousness because one of ordinary skill in the art could not have had access to the unknown subject matter, and, therefore, could not have relied on the unknown subject matter in the prior art to practice the claimed invention. Therefore, without the benefit of impermissible

hindsight, an unknown inherency in a prior art reference cannot be the basis of a *prima facie* case of obviousness.

In this case, not only was it unknown that Slit2 inhibited HMVEC migration at the time of the application, the possibility of Slit2 inhibiting HMVEC was not even present in the prior art because Geng teaches directly away from the use of Slit2 for inhibiting HMVEC migration. According to §2112 (IV) of the MPEP, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." (Citing *In re Rijckaert*, 9 F.3d at 1534, 28 USPQ2d at 1957 (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art). Furthermore, the MPEP § 2112 (IV) quotes the CAFC stating that "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Geng does not make it clear that HMVEC migration may be inhibited with Slit2, and therefore, it does not establish inherency of the same. As such, the subject matter of the current claims was not, in fact, inherent in the cited reference. (See, e.g., MPEP 2112(II) "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp.*, 339 F.3d at 1377, 67 USPQ2d at 1668).

It was only after the work performed by the current inventors, that the inhibition of HMVEC migration by Slit2 was discovered. More specifically, the current application discloses examples that show that Slit2 inhibits HMVEC migration and these findings were the result of inventive efforts on the part of the applicants. These findings challenge the teachings of Geng and show that Slit2 actually has the opposite effect as that disclosed by Geng. Therefore, only with impermissible hindsight, the benefit of applicants' disclosure, and reliance on an unknown inherency, would it be possible for

one of ordinary skill in the art to act in contravention to the teachings in the cited art to arrive at the subject matter claimed in the present claims. .

Part of a *prima facie* case of obviousness includes "[s]ome teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or combine prior art reference teachings to arrive at the claimed invention." (MPEP, § 2143). A *prima facie* case of obviousness may also include combining prior art elements according to known methods to yield predictable results, applying a known technique to yield predictable results, and choosing from predictable solutions with reasonable expectation of success. *Id.* However, there would have been no motivation, predictable results, or reasonable expectation of success for one of skill in the art to try and use the teachings of Geng to inhibit HMVEC migration using Slit2. The only prediction or reasonable expectation in view of Geng would be that Slit2 would promote HMVEC migration, exactly the opposite result required by the subject matter recited in current claims (see, e.g., paragraph [0014] and FIG. 2 of Geng). The fact that applicants' discovery runs contrary to the understandings forwarded by Geng and establishes that Slit2 inhibits migration of HMVECs is the touchstone of patentability and only highlights the significance of the claimed invention.

Despite the obvious shortcomings of Geng, the Examiner on page 10, lines 14-16 of the Office Action, alleges that inhibiting the migration of HMVECs would naturally flow from following the teachings of Geng in view of Goldberg. Yet it bears emphasizing, Geng teaches only promoting the migration of HMVECs by using Slit2. Geng does not teach and could never be understood to teach the inhibition of HMVEC migration through the use of Slit2 as required by the pending claims. Accordingly, one of skill in the art, after reading Geng, would expect that exposing HMVECs to Slit2 could only induce the migration of the HMVECs. This teaching of Geng is directly contradictory to the current claims 7 and 9 that are directed to a method of inhibiting the migration of HMVECs. In fact, Geng teaches directly away from the claimed invention by teaching that Slit2 induces HMVEC migration. Therefore, contrary to what has been asserted by the Examiner, the current claims do not "naturally flow from following the teaching of Geng in view of Goldberg."

For the foregoing reasons, applicants respectfully request the withdrawal of the rejection of claims 7 and 9 under § 103.

Conclusion

It is believed that all of the claims are patentable in their present form and a prompt notice of allowance for this application is respectfully requested. If the Examiner finds any remaining impediment to the prompt allowance of this application, please contact the undersigned attorney.

Respectfully submitted,

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